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Vroon, Pieter; Roosblad, Jimmy; Poese, Fauzia; Wilschut, Jan; Codrington, John; Vreden, Stephen; Zonneveld, Rens

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Case study

Severity of acute Zika virus infection: A prospective emergency room surveillance study during the 2015–2016 outbreak in Suriname

Pieter Vroon[a], Jimmy Roosblad[b], Fauzia Poese[c], Jan Wilschut[h], John Codrington[b], Stephen Vreden[d,e], Rens Zonneveld[f,g,i,*]

[a] Erasmus University, Rotterdam, The Netherlands
[b] Clinical Laboratory, Academic Hospital Paramaribo, Paramaribo, Suriname
[c] Emergency Department, Academic Hospital Paramaribo, Paramaribo, Suriname
[d] Department of Internal Medicine, Academic Hospital Paramaribo, Paramaribo, Suriname
[e] Center for Excellence for Neglected Infectious Diseases, Academic Hospital Paramaribo, Paramaribo, Suriname
[f] Scientific Research Center Suriname, Academic Hospital Paramaribo, Paramaribo, Suriname
[g] Department of Pediatrics, Academic Hospital Paramaribo, Paramaribo, Suriname
[h] Department of Virology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[i] Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

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ABSTRACT

Acute Zika virus (ZIKV) infection is usually mild and self-limiting. Earlier, we reported three cases of fatal acute ZIKV infection in patients without typical signs of ZIKV, but rather with criteria of systemic inflammation response syndrome (SIRS). To follow up these observations, we prospectively included patients at the emergency room with temperature instability and suspected to have acute ZIKV infection, SIRS, or both. A total of 102 patients were included of whom N = 21 (21%) were suspected of acute ZIKV infection, N = 56 (55%) of acute ZIKV infection with SIRS criteria, and N = 25 (24%) of SIRS alone. ZIKV-PCR was positive in N = 21 (20%) patients. Eight (38%) ZIKV-positive patients needed admission to the hospital of whom four (50%) presented with SIRS alone. One ZIKV-positive patient had vascular co-morbidity and died following shock and severe coagulopathy. We confirm the hypothesis that acute ZIKV infection can present atypical and severely with systemic inflammation and have lethal course particularly amongst patients with significant prior disease.

Introduction

Zika virus (ZIKV) infection, a mosquito-borne febrile illness similar to Dengue has spread rapidly through the Americas from 2015 into 2016 [1,2]. In Suriname, the first cases of ZIKV were recognized in September 2015 [3]. Most adult patients have no signs of acute ZIKV infection. For patients with signs of ZIKV the case definition comprises a mild and self-limiting triad of fever, maculopapular rash and polyarthritis. Since its arrival in the Americas, ZIKV infection is associated with atypical Guillain-Barre syndrome in adults and with brain malformations in newborns, indicating increased virulence potential [4,5].

In an earlier case series, we described three adult patients without typical signs of acute ZIKV infection, but rather with symptoms of systemic inflammation response syndrome (SIRS) and critical illness [6]. All three patients died rapidly with ZIKV being the only microbiological presence, confirmed by real time-polymerase chain reaction (RT-PCR). It remains speculative if ZIKV alone, or a downwards spiral of pre-existing disease initiated by ZIKV, was the culprit in their fatal outcome of these cases. Several other American countries, such as Colombia and Brazil, have also reported similar atypical and lethal cases of ZIKV infection amongst adults, both with and without comorbidity or co-infection [7–11]. These and our data indicate that acute ZIKV infection can lead to critical illness and death, which was formerly unknown [2]. Potentially, due to absence of signs of the currently accepted case definition for ZIKV, severe cases of acute ZIKV infection have gone unnoticed during earlier outbreaks.

To investigate the severity of acute ZIKV infection, we conducted a prospective study in the Academic Hospital in Paramaribo, Suriname. We included adult patients at the emergency room, presenting with a history and/or signs of ZIKV infection, SIRS criteria, or both. We hypothesized that acute ZIKV infection can present with symptoms of SIRS, often accompanied with poor outcome defined as need for hospitalization and death.

* Corresponding author at: Academic Hospital Paramaribo, Flustraat 1, Paramaribo, Suriname.
E-mail address: rens.zonneveld@gmail.com (R. Zonneveld).

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Methods

Study design

Suriname is a small multiethnic country on the northeast corner of South America with a population of approximately 550,000 inhabitants, half of whom live in the capital city Paramaribo. The emergency room of the Academic Hospital Paramaribo serves as the only ER in Suriname. During a one-month period in March 2016, trained medical students, residents and nurses performed around-the-clock surveillance at the emergency room for inclusion of eligible patients for this prospective cross-sectional study.

We included patients above 16 years of age with a history or clinical presentation of temperature instability (*i.e.*, body temperature < 36 °C or > 38 °C) with either (i) Suspected ZIKV infection, defined as a history and/or clinical presentation with, at least one clinical sign of acute ZIKV infection (*i.e.*, maculopapular rash, myalgia, arthralgia/arthritis, conjunctivitis), or (ii) Suspected ZIKV infection with SIRS criteria, defined as presentation with history and/or clinical sign of both acute ZIKV infection with at least one SIRS criterium (*i.e.*, a heart rate above 90 beats/min, respiratory rate above 20/min, leukocyte counts < 4 or > 12×10^9/L), or (iii) SIRS, defined as presentation with at least one SIRS criterium without history and/or clinical sign of acute ZIKV infection. Blood gas analysis was not performed routinely at inclusion and not used as SIRS and inclusion criterium.

Upon clinical indication routine laboratory testing, serology (*i.e.*, HIV, leptospirosis, and/or dengue), and bacterial culturing (*i.e.*, blood, urine, and/or faeces) were performed. ZIKV PCR on serum and/or urine was performed on stored serum at the Academic Hospital Paramaribo. Appropriate written informed consent was obtained from the study subjects or their guardians. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. We received approval for this study from the Surinamese Ethical Board (VG 007-16).

Data and sample collection

The following data were recorded with a standardized questionnaire: patient age, sex, prior medical history and comorbidity (summarized in the McCabe classification [12]), medication including recent antibiotics, onset of symptoms and exact current symptomatology. Also recorded were physical examination, results from laboratory testing, serology, and culturing, and course of disease (*i.e.*, need for hospitalization, duration of hospital stay and/or death). Trained nurses, students or residents collected whole blood in serum vacutainers by vena puncture at presentation of the patients in the ER. Blood was used for routine determination of chemical and haematological markers, serology, and blood culturing at the Academic Hospital Paramaribo, where indicated. Serum was separated by centrifugation at 2500 × *g* for 8 min at room temperature and then residual serum was stored immediately at −80 °C for later ZIKV PCR. Urine samples were collected at the ER and used for routine urinalysis, bacterial culturing, and stored samples for later ZIKV PCR.

Sample analysis

Real time polymerase chain reaction

ZIKV RT-PCR was performed as described before [6] by two technicians. ZIKV RNA was extracted from 150 µl of each specimen by using the E.Z.N.A. Viral RNA Kit (OMEGA Bio-Tek), according to the manufacturer's instructions. PCR was performed with SYBR Green I (Thermo Scientific, Verso SYBR Green) for detection.

Serology

All serology was performed as described before [6]. In short, CHIKV serology was performed with Anti Chikungunya Virus IIFT kit (Euro-Immun) according to the manufacturer's instructions and DENV serology was performed with RapidSignal Dengue IgG/IgM (Orgenics) according to the manufacturer's instructions; HIV serology was performed with ELISA (Architect) and Leptospirosis serology was performed with Leptochec (Zephyr Biomedicals), both according to the manufacturer's instructions.

Statistical analysis

Incidence rates end epidemiological determinants were calculated. Categorical variables were presented as numbers and percentages and continuous variables, due to the non-Gaussian distribution, as median with interquartile range. Categorical data were compared with chi-square and continuous variables with a Mann-Whitney *U* test.

Results

Baseline characteristics of the study group

A total of 102 patients were included of whom N = 21 (21%) presented with suspected ZIKV infection, N = 56 (55%) with suspected ZIKV infection with SIRS criteria, and N = 25 (24%) with SIRS criteria alone (Table 1). Patients with SIRS criteria were hospitalized more ($P < 0.05$) and more positive blood cultures were found in the acute ZIKV with SIRS criteria group than in the other groups ($P < 0.05$). Further baseline characteristics, including positive ZIKV PCR, were similar between the three groups. Of all patients, N = 43 (42%) were admitted to the hospital. Two patients died of whom one had acute ZIKV infection presenting with just symptoms of SIRS.

Table 1
Baseline characteristics of 102 patients at the Emergency Room in Suriname.

Patient Characteristics		Suspected Zika (N = 21)	Suspected Zika with SIRS Criteria[a] (N = 56)	SIRS Criteria[a] (N = 25)	Total Cohort (N = 102)
Baseline Characteristics	Median age, y (range)	48 (19–67)	45 (17–95)	48 (17–86)	46 (17–95)
	Female sex	14 (67)	34 (61)	16 (64)	64 (63)
Microbiology	Positive ZIKV RT-PCR	5 (25)	11 (20)	5 (20)	21 (21)
	Positive Blood Culture	1	8 (14)	1	10 (10)
Outcomes	Not hospitalized	19 (90)	29 (52)	11 (44)	59 (59)
	Hospitalized[b]	2 (10)	27 (48)	14 (56)	43 (41)
	- *Median duration of stay, d (range)*	7 (4–10)	6.5 (1–16)	6.5 (3–45)	6.5 (1–45)
	- *7-day mortality*	0	1	1	2 (1)

SIRS = systemic inflammatory response syndrome; RT-PCR = real time polymerase chain reaction; ZIKV = Zika virus; NA = Not applicable.
Data presented as N (%), except as indicated.

[a] SIRS criteria defined as a heart rate above 90 beats/min, respiratory rate above 20/min, leukocyte count < 4 or > 12×10^9/L.

[b] Admission was either on the Internal Ward, Cardiac Care Unit, or Intensive Care Unit.

Table 2
Characteristics of 102 patients at the Emergency Room in Suriname, by Zika PCR result.

Patient Characteristics < N/N >		Negative Zika (N = 81)	Positive Zika[a] (N = 21)	P-value
Baseline Characteristics	Median age, y (IQR) < 79/21 >	46 (31–59)	46 (37–74)	
	Stratified Age, < 80/21 >			
	- *18–29y*	21 (26)	5 (24)	
	- *30–49y*	20 (25)	8 (38)	
	- *50y or older*	39 (49)	8 (38)	
	Female sex	51 (63)	13 (62)	
	Pre-existing comorbidity < 80/21 >			
	- *None*	19 (24)	11 (52)	< 0.01
	- *Hypertension*	24 (30)	6 (29)	
	- *Diabetes Mellitus*	14 (18)	3 (14)	
	- *Heart disease*	0 (0)	1 (5)	< 0.05
	- *Chronic Disease*[b]	8 (10)	5 (24)	
	- *Cancer*	3 (4)	2 (10)	
	- *Sickle Cell*	3 (4)	1 (5)	
	- *HIV*	7 (9)	1 (5)	
	McCabe Class 1	59 (74)	10 (48)	< 0.05
Patient history	Median duration of symptoms, d (IQR) < 78/18 >	2 (1–5)	3 (2–8)	< 0.01
	Fever	76 (94)	9 (43)	
	Arthralgia	46 (57)	9 (43)	
	Myalgia	45 (56)	15 (71)	
	Rash	8 (10)	4 (19)	
	Conjunctivitis	12 (15)	3 (14)	< 0.05
	Headache	65 (80)	12 (57)	
	Nausea, vomiting and/or diarrhea	59 (73)	16 (76)	
	Oliguria or anuria	8 (10)	5 (24)	
	Prior antibiotics < 79/21 >	14 (18)	2 (10)	
Physical Examination	Fever (body temperature above 38 °C)	30 (37)	6 (30)	
	Median body temperature, °C (IQR)	37.8 (36.6–38.6)	37.0 (35.6–38.4)	
	Median Respiratory rate (IQR) < 71/17 >	20 (18–24)	20 (18–23)	
	Median Heart rate (IQR) < 79/21 >	104 (88–119)	89 (83–106)	< 0.01
	Median Blood pressure (sys/dia) < 80/21 >	120/80	118/72	
	Arthritis	3 (4)	2 (10)	
	Rash	6 (7)	4 (19)	
	Edema	2 (2)	2 (10)	
	Petechiae and/or ecchymosis	0	1 (5)	
	Coma (EMV < 8)	0	0	
Laboratory data, median (IQR)	WBC Day 1 < 79/19 >	9 (6–12)	10 (6–17)	
	PMN Day 1, % < 57/14 >	75 (59–81)	73 (67–90)	
	Platelets < 78/19 >	226 (162–291)	250 (211–349)	
	CRP < 76/19 >	4 (1–14)	2 (1–7)	
	Albumin < 27/4 >	30 (26–33)	25 (19–30)	
	Creatinine < 79/18 >	83 (65–112)	73 (59–100)	
Microbiology	Positive Blood Culture < 36/6 >	7 (19)	3 (50)	
	Leptospirosis < 10/0 >	4 (40)	0 (0)	
	Dengue IgG antibodies < 8/1 >	3 (38)	1 (100)	
	HIV < 13/2 >	2 (15)	0 (0)	
Clinical Course	Not hospitalized	45 (56)	13 (62)	
	Hospitalized[c]	36 (44)	8 (38)	
	- *Median duration of stay, d (IQR)*	6.5 (4.3–12.3)	5.5 (1.8–9)	
	- *Mortality*	1	1	

WBC = white blood cell count; PMN = polymorphonuclear cells; CRP = C-reactive protein; HIV = human immunodeficiency virus.
Data presented as N (%), except as indicated. P-values are given when significant (P < 0.05).
[a] N = 17 ZIKV PCR positive results in serum and N = 4 in urine.
[b] Chronic disease: Migraine, anaemia, drug abuses, epilepsy, asthma, kidney disease, cerebrovascular accident or transient ischemic attack.
[c] Admission was either on the Internal Ward, Cardiac Care Unit, or Intensive Care Unit.

Characteristics of ZIKV-positive patients

Of all patients, n = 81 (80%) had a negative ZIKV PCR and n = 21 (20%) a positive ZIKV PCR result, the latter being positive in either serum (n = 17) or urine (n = 4) (Table 2). A total of 16 (76%) ZIKV-positive patients presented with SIRS criteria, of whom N = 5 (31%) with SIRS criteria alone. Patients with a positive ZIKV PCR presented more often without comorbidity than the ZIKV-negative patients (P < 0.01). Fever was less commonly reported in patients with a positive *versus* negative ZIKV PCR (P < 0.01). Further patient history, physical examination, or results from laboratory testing did not discriminate between negative and positive ZIKV PCR.

Severity and outcomes of acute ZIKV infection

Of 21 patients with a positive ZIKV PCR, n = 13 (62%) were not hospitalized and discharged home directly from the ER and n = 8 (38%) were admitted to the hospital of whom one directly to the ICU (Table 3). Of these admitted patients n = 4 (50%) presented with SIRS criteria alone. Seven admitted patients recovered and were discharged home. One ZIKV-positive patient presented with just symptoms of SIRS and shock (blood pressure 60/40 mmHg), leucocytosis (16.1×10^9/L with 90.3% granulocytes), raised CRP (29.3 mg/dL), thrombocytopenia (125×10^9/L), and signs of coagulopathy (*i.e.*, ecchymosis). This patient had significant prior disease (*i.e.*, diabetes mellitus, hypertension

Table 3
Characteristics of 21 ZIKV positive patients, by need for hospitalization.

		Not hospitalized (N = 13)	Hospitalized[a] (N = 8)	P-value
Baseline Characteristics	Median age, y (IQR)	45 (29–75)	48 (43–72)	
	Stratified Age			
	- *18–29y*	4 (31)	1 (13)	
	- *30–49y*	5 (38)	3 (38)	
	- *50y or older*	3 (23)	4 (50)	
	Female sex	10 (77)	3 (38)	
	Pre-existing comorbidity			
	- *None*	8 (62)	3 (38)	
	- *Hypertension*	2 (15)	4 (50)	
	- *Diabetes Mellitus*	0	3 (38)	< 0.05
	- *Heart disease*	0	1 (13)	
	- *Chronic Disease*	2 (15)	3 (38)	
	- *Cancer*	2 (15)	0	
	- *Sickle Cell*	0	0	
	- *HIV*	1 (8)	1(13)	
	McCabe Class 1	13 (100)	8 (100)	
Patient history	Median duration of symptoms, d (IQR)	2 (1–3)	5 (3–14)	< 0.05
	Fever	10 (77)	8 (100)	
	Arthralgia	7 (54)	2 (25)	
	Myalgia	10 (77)	5 (63)	
	Rash	3 (23)	1 (13)	
	Conjunctivitis	2 (15)	1 (13)	
	Headache	8 (62)	6 (75)	
	Nausea, vomiting and/or diarrhea	8 (62)	6 (75)	
	Oliguria or anuria	2 (15)	3 (38)	
	Prior antibiotics < 13/8 >	1 (8)	1 (13)	
Physical Examination	Fever (body temperature above 38 °C)	3 (23)	3 (38)	
	Median body temperature, °C (IQR)	36.8 (35.7–38.1)	37.4 (35.4–38.9)	
	Median Respiratory rate (IQR)	18 (16–20)	21 (18–26)	
	Median Heart rate (IQR)	89 (83–100)	101(80–113)	
	Median Blood pressure (sys/dia)	121/76	116/68	
	Arthritis	2 (15)	0	
	Rash	3 (23)	1 (13)	
	Edema	2 (15)	0	
	Petechiae and/or ecchymosis	0	1 (13)	
	Coma (EMV < 8)	0	0	
Laboratory data, median (IQR)	WBC Day 1 < 11/8 >	8 (6–14)	15 (7–29)	
	PMN Day 1, % < 7/7 >	68 (66–75)	89 (72–90)	
	Platelets < 11/8 >	250 (211–349)	272 (207–357)	
	CRP < 11/8 >	2 (1–3)	7 (1–29)	
	Albumin < 0/4 >		25 (19–30)	
	Creatinine < 10/8 >	62 (57–75)	93 (76–122)	
Microbiology	Positive Blood Culture < 1/5 >	1	2 (40)	
	Leptospirosis < 0/1 >	0	0	
	Dengue IgG antibodies < 0/1 >	0	1 (100)	
	HIV < 0/2 >	0	0	

WBC = white blood cell count; PMN = polymorphonuclear cells; CRP = C-reactive protein; HIV = human immunodeficiency virus.
Data presented as N (%), except where indicated. P-values are given when significant (P < 0.05).
[a] Admission was either on the Internal Ward, Cardiac Care Unit, or Intensive Care Unit.

and a coronary artery bypass grafting) and died after two days of admission to the ICU. Of the ZIKV-positive admitted patients one patient also tested positive for *Shigella*.

Discussion

This prospective study was performed during the 2015–2016 ZIKV epidemic in Suriname to investigate whether acute ZIKV infection can present with symptoms of SIRS in addition to or instead of typical symptoms of ZIKV infection. Amongst 102 patients, ZIKV PCR was positive in 20% of whom 33% presented with SIRS criteria and 25% had no history or clinical signs of acute ZIKV infection. The clinical course of ZIKV-positive patients varied from immediate discharge from the emergency room to requiring hospitalization and death. Overall, this study confirms that acute ZIKV infection can take an atypical, severe and even lethal course, also described in earlier case reports from our group and others [6–11].

This is the first study that prospectively investigated severity of acute ZIKV infection. Since the arrival of ZIKV in South America, and the first reports on fetal neurodegenerative effects of ZIKV infection during pregnancy and the association with atypical cases of Guillain-Barre in adults, there has been much debate on underlying mechanisms of increased virulence potential of ZIKV. ZIKV, identified as such in the 1950s, has been known for many years as a mild and self-limiting disease and 70–75% of patients with ZIKV usually remain asymptomatic [13,14]. It is, at least, puzzling that there are few, if any, reports of severe or lethal acute ZIKV reported in earlier. Some speculations to its increased virulent potential have been posed, such as viral factors (*e.g.*, genetic shift, mutation) [15], host factors (*e.g.*, underlying disease or circulating antibodies against DENV, a Flavivirus similar to Zika), and environmental factors (*e.g.*, local use of pesticides) [2,16–18]. All of these options for severe disease remain hypothetical, even if they are in some cases supported by *in vitro* and *in vivo* experimental data.

A final and plausible option is that ZIKV infection has been presenting severely without typical, generally acknowledged, signs of ZIKV. In those cases, acute ZIKV infection as the cause of a patient's

severe or lethal disease remains unnoticed and not likely to be considered by clinicians. Indeed, in our study half of the severe cases of acute ZIKV infection presented without typical symptoms of ZIKV infection. Proper recognition of ZIKV is further complicated by the fact that testing for ZIKV remains difficult, due to absence of sensitive serological testing and the short window during which the ZIKV PCR is positive amongst infected individuals.

Currently, there is a lack of data on the potential of ZIKV to cause systemic inflammation. Only one study has reported cytokine levels in patients; in this study differences between acute and reconvalescent phases of ZIKV infection were found [19]. During severe systemic inflammation several responses are well known and consistently observed, which have also been observed in the lethal cases from our earlier case series and the fatal case observed in this study [6]. These include increases in numbers and aberrant activation of leukocytes, raised infection parameters, coagulopathy, oedema, hypotension, multi-organ failure, and ultimately death [20]. Illustratively, especially DENV is known to have the potential to cause an intravascular cytokine storm and increased endothelial permeability without cellular damage, both seemingly underlying systemic inflammation and septic shock [21]. A similar mechanism could be involved in acute ZIKV infection. Additionally, underlying disease may predispose to a severe course of the disease. Indeed, all lethal cases in Suriname were male patients above 50 years of age with prior vascular disease, hypertension and diabetes mellitus. Interestingly, in earlier studies on DENV infection, presence of hypertension and diabetes mellitus was associated with transition of Dengue Fever into severe systemic inflammation and lethal Dengue Hemorrhagic Fever [22]. Potentially, an entity for acute ZIKV infection similar to Dengue Hemorrhagic Fever exists. Since ZIKV and DENV are related viruses, both belonging to the family *Flaviviridae*, this is not unlikely. Overall, from our data, there is strong indication that a combination of both viral and host factors is likely to cause systemic inflammation and critical illness in patients with acute ZIKV infection. More prospective studies with further analysis of viral factors, such as viral loads, and host-responses, such as measurement of intravascular cytokines, are necessary to further unravel the potential of ZIKV to cause systemic inflammation.

There is a possibility that the presence of a co-infection is co-determining the severity of the clinical course of ZIKV infection. Two patients that were hospitalized with a positive ZIKV PCR also had a positive blood culture. One of the admitted patients in our database had a co-infection with *Shigella* and appeared more ill than usual for such an infection and needed to be admitted to the hospital. It is also known that leptospirosis can co-exist in febrile patients with dengue and cause exacerbated disease and that acute severe viral infections can be complicated with bacterial septic shock [23,24]. Last, *in vivo* work in mice indicates that presence of DENV IgG antibodies can exacerbate the severity of ZIKV infection [25]. One patient in the current cohort that needed hospitalization had IgG antibodies against DENV. Further clinical evidence is needed to strengthen this hypothesis, which can be gathered in similar studies like the current one.

The present study does have some important limitations. First, the ZIKV epidemic in Suriname was waning in March 2016, when this study was performed. This led to a relatively small study cohort. Second, due to ethical constraint, we were not able to include patients not presenting at the ER or without temperature instability at our ER, which could have resulted in a selection bias. Third, due to the absence of a serological test for Zika, we may have underestimated the true amount of ZIKV positive patients. Last, in many ZIKV patients serology for other infectious diseases was not performed, which may have underestimated presence of those.

In conclusion, acute ZIKV infection can present with systemic inflammation and severe disease. During future outbreaks, increased vigilance for a severe and potentially lethal course of disease is warranted, particularly amongst patients with significant prior vascular prior disease. Further research into underlying mechanisms of severe course of acute ZIKV infection is necessary.

Conflicts of interest

The authors report no conflict of interest.

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